Summary of Safety and Effectiveness Data (SSED)

I. GENERAL INFORMATION

Device Generic Name: Rechargeable vagal blocking system

Device Trade Name: MAESTRO® Rechargeable System

Device Procode: PIM

Applicant's Name and Address: EnteroMedics, Inc.

2800 Patton Road St. Paul, MN 55113

Date of Panel Recommendation: June 17, 2014

Premarket Approval Application (PMA) Number: P130019

Date of FDA Notice of Approval: January 14, 2015

II. INDICATIONS FOR USE

The MAESTRO® Rechargeable System is indicated for use in weight reduction in patients aged 18 years through adulthood who have a Body Mass Index (BMI) of 40 to 45 kg/m², or a BMI of 35 to 39.9 kg/m² with one or more obesity related co-morbid conditions, and have failed at least one supervised weight management program within the past five years.

III. <u>CONTRAINDICATIONS</u>

The MAESTRO® Rechargeable System is contraindicated in individuals who:

- Have cirrhosis of the liver, portal hypertension, esophageal varices or a clinically significant hiatal hernia;
- Plan on needing magnetic resonance imaging (MRI);
- Plan on needing shortwave, microwave, or therapeutic ultrasound diathermy;
- Are at high risk for surgical complications;
- Have a permanently implanted, electrical powered medical device, or gastrointestinal device or prosthesis (e.g., pacemakers, implanted defibrillators, or neurostimulators).

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IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the MAESTRO® device labeling.

V. <u>DEVICE DESCRIPTION</u>

The MAESTRO® Rechargeable System is comprised of implantable and external device components, which are listed in Table 1:

Table 1: MAESTRO® Rechargeable system components

Implantable Component	Model numbers
Rechargeable Neuroregulator (RNR)	Model 2002
Posterior Lead-Marked	Model 2200P-47E
Anterior Lead-Unmarked	Model 2200A-47E

External Components	Model numbers
Mobile Charger (MC)	Model 2402
Patient Transmit Coil	Model 2403-60, Model 2403-60A
Clinician Transmit Coil	Model 2403-300
Clinician Programmer (CP)	Model 2502
Programmer Cable	Model 1600
AC Recharger	Model 1620
Patient Transmit Coil Belt	Model 1660, Model 1660A
Transmit Coil Foam Pad	Model 1670
Torque Wrench	Model 1680

The MAESTRO System provides vagal blocking (VBLOC®) therapy by delivering intermittent, controllable electrical blocking signals to the abdominal anterior and posterior abdominal nerve trunks of the vagus nerve.

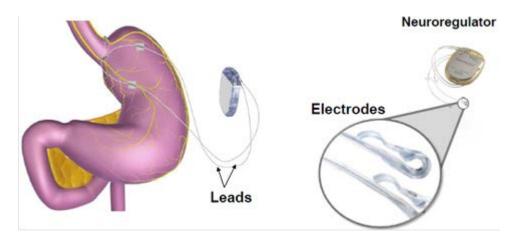


Figure 1. MAESTRO[®] Rechargeable Neuroregulator and leads, with placement of the electrodes on the abdominal anterior and posterior nerve trunks.

The MAESTRO System is intended to promote weight loss by applying electrical pulse algorithms which block signals to the anterior and posterior trunks of the intra-abdominal vagus nerve. Other intended weight-reducing effects of electrical neural blockade include:

- Reduced food intake by reducing gastric accommodation;
- Promoting satiety by delaying food processing and gastric emptying;
- Decreasing caloric intake.

The System is designed to deliver square, biphasic, charge balanced, constant current to the abdominal nerve trunks (current range, 0-8 mA) at a pulse frequency of 5000 Hertz and a pulse width of 90 microseconds. The maximum charge density (8 mA) is estimated to be $5.3~\mu\text{C/cm}^2$.

Model 2002 Pulse Generator

The Model 2002 Pulse Generator (RNR) is provided sterile and has a hermetic case enclosure with an integrated coil that acts as the telemetry and recharging antenna. The RNR is surgically implanted subcutaneously on the thoracic sidewall. The principal function of the RNR is to deliver current to the leads. It contains a Rechargeable 2.6 AH Li-ion battery (8 year battery life). When recharging, the mobile charger and transmit coil transfer power to the RNR and exchange information via a low power inductive telemetry link with a range of less than 5 cm. Power is transferred by emitting a continuous wave signal at 6.78 MHz, centered in the 6.765-6.795 MHz Industrial, Science and Medical (ISM) radio band. It is recharged transcutaneously using the transmit coil. The RNR is labeled as unsafe for magnetic resonance imaging (MRI).

Model 2200-47E Leads (Anterior and Posterior)

The Model 2200-47E Leads are provided sterile and are flexible and are approximately 47 cm in length. They contain bipolar platinum/iridium tip & ring electrodes with an insulated lead body. The tip (i.e., nerve) electrode contains rigid (316L) stainless steel encased in silicone to provide structural support. Current is delivered to the nerve electrode via 90/10 platinum/iridium electrodes. A suture tongue anchors and stabilized the nerve electrode. The tip electrode measures lead impedance and delivers electrical pulses to the vagus nerve trunks. The ring electrode is sutured to the stomach, and is used for measuring lead impedance. The leads are placed on the anterior and posterior intra-abdominal nerve trunks. Unlike the helical or closed cuff designs used with other peripheral nerve stimulation electrodes, the MAESTRO leads are "C" shaped, and cradle rather than wrap around the abdominal vagus nerve trunks. Sutures anchor and stabilize lead placement. The leads are also labeled as unsafe for MRI.

Model 2402 Mobile Charger

The Model 2402 Mobile Charger (MC) is provided non-sterile and is powered by a rechargeable, lithium-ion battery which is recharged using the AC Recharger connected to a power outlet. The MC can be left plugged in to the AC Recharger when not used for recharging the RNR. When the MC battery is full, the AC recharger will stop charging. Patients are required to recharge the RNR battery as indicated by the display

on the MC. The MC recharges the RNR when connected to the transmit coil positioned over the RNR. The MC uses the same connection to the AC recharger as the Patient Transmit Coil. Therefore, the Mobile Charger cannot be simultaneously connected to both the Patient Transmit Coil and the AC Recharger, thus insuring that the Transmit Coil cannot be connected when the MC is connected to an AC source of current. Patients are required to check the battery daily and recharge when needed.

Transmit Coils

There are three (3) different transmit coils available. These transmit coils are provided sterile.

Model 2403-300 Clinician Transmit Coil

The Model 24030300 Clinician Transmit Coil is for use in the operating room with the MAESTRO[®] Rechargeable System. The Clinician Transmit Coil is placed within a sterile sleeve for use in the operating room.

Model 2430-60 Patient Transmit Coil

The Model 2430-60 Patient Transmit Coil is for patient use with the MAESTRO[®] Rechargeable System and is five (5) inches in diameter with a 60cm long cable. The standard coil supplied in the implant kit has silicone as the skin contacting material (Model 2403-60). A second coil (Model 2403-60A) is available, which has an outer jacket of compressed foam and is otherwise identical to Model 2430-60. Physicians may request this coil if they decide it is better suited for a particular patient. Both transmit coils may be used with the optional Model 1670 Foam Pad to assist in achieving the desired spacing of 2-3cm between the transmit coil and the implanted neuroregulator to optimize recharging efficiency.

Model 2430-60A Patient Transmit Coil

The Model 2430-60A Patient Transmit Coil is identical to the Model 2430-60 device component, but has an optional foam pad to assist in achieving the desired spacing between the transmit coil and the implanted neuroregulator.

Model 2501 Clinician Programmer

The Model 2501 Clinician Programmer is a non-sterile, external, programmable, ambulatory microprocessor and controller with compatible, customized firmware. The commercially available laptop is used by the clinician to modify therapy parameters and treatment schedule. It transmits information to the Mobile Charger and uploads data from the Mobile Charger.

Customized Software

Software is provided with the Model 2501 Clinician Programmer/laptop computer and enables communication with the Mobile Charger and neuroregulator. The CP allows physicians to modify therapy parameters and delivery schedules and retrieve diagnostic information. Sample settings are set using the Clinician Programmer.

Therapy Algorithms

The MAESTRO system delivers pulses of current to vagal nerve trunks at a high frequency, which maintains the nerve fibers in a refractory state and suppresses the natural impulses that are conveyed from the periphery (i.e., stomach) to the brain stem and higher centers of the central nervous system (CNS).

Programmer Cable Description

The Model 1600 Programmer Cable is non-sterile and is used to provide connectivity between the Model 2502 Clinician Programmer and the Model 2402 Mobile Charger.

AC Recharger Description

The Model 1620 AC Recharger is a non-sterile power supply used for charging the Mobile Charger battery. The AC Recharger is provided with an appropriate power cord to accommodate the electrical mains connection for the geographic location (Part Number P00899-001 for North America). The AC Recharger uses the same connection to the Mobile Charger as the Transmit Coil. Therefore, the Mobile Charger cannot be used to recharge the RNR when it is connected to the AC Recharger.

Patient Transmit Coil Belt Description

The Patient Transmit Coil Belts are non-sterile, external accessories that may be used to assist in holding the patient transmit coil over the location of the implanted RNR during charging. The Model 1660 Transmit Coil Belt is for use with the Model 2403-60 Patient Transmit Coil and the Model 1660A Transmit Coil Belt is for use with the Model 2403-60A Patient Transmit Coil.

Transmit Coil Foam Pad Description

The Model 1670 Transmit Coil Foam Pad is an optional non-sterile external accessory that may be used to assist in achieving the desired spacing between the patient's Transmit Coil and the implanted neuroregulator to optimize recharging efficiency.

Torque Wrench Description

The Model 1680 Torque Wrench is a sterile standard surgical wrench provided for use during the implant procedure to tighten set screws that secure the leads to the RNR as described in the implant procedure guide instructions for use.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternatives for the treatment of obesity. These alternative treatments include lifestyle interventions, such as behavioral therapy (e.g., diet and exercise), pharmacotherapy (e.g., phentermine based drugs), other medical devices (e.g., Lap Band®), and surgery (e.g., gastric bypass or sleeve gastrectomy). There are currently limited options for morbidly obese patients. Pharmacotherapy trials have generally demonstrated a \geq 7-13% total weight loss from initial body weight after subtracting for the placebo effect, but some patients have experienced adverse systemic side effects¹. Gastric bypass surgery is among the most effective means of obtaining durable and clinically significant weight loss, but can result in serious complications, including

perforation, hemorrhage, infections and bowel obstructions². The Lap Band® is also effective in providing long-term weight loss, but can produce adverse events of band prolapse and band erosion².

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The MAESTRO® Rechargeable System received CE Mark for the treatment of obesity in March 2011 and has been listed on the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA) for supply in Australia.

The MAESTRO® Rechargeable System has not been marketed in the United States.

The MAESTRO® Rechargeable System has not been withdrawn from any market.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with use of the device:

- Allergic or immune responses to the implanted materials that could results in device rejections;
- Pain at the neuroregulator and/or lead site, resulting from infection, skin irritation, wound dehiscence, erythema, erosion of the neurostimulator, seroma and hematoma:
- Malfunction of the components of the MAESTRO Rechargeable System, including loss of therapy, lead migration, lead fracture, lead dislodgement, and bowel entanglement with the leads;
- Device or therapy-related events, including heartburn/dyspepsia, abdominal pain, dysphagia (swallowing difficulty), belching, nausea and chest pain;
- Damage to the vagal nerve trunks.

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

The MAESTRO[®] Rechargeable System and individual system components were evaluated using internationally accepted, and FDA recognized, standards for performance testing. General tests and conformance to specifications were performed for implantable components and accessories, including:

- Visual inspection
- Device marking requirements, per EN 45502-1: 1998, EN 45502-2-1:2003, and ISO 58413:2000
- Kit and component packaging, and shipping and temperature conditioning per ASTM D4169.

Samples were preconditioned prior to bench testing, including:

- Thermal Shock: The neuroregulator and leads were required to withstand a temperature/shock cycling, from -10°C to 55°C.
- Environmental conditioning (shock, vibration, pressure, temperature): Temperature and humidity cycling per EN 45502-1: 1998.
- Shipping simulation and temperature conditioning: Package free fall, loose load, and random vibrations after cycling between -10°C ± 3°C and 55°C ± 2°C per ASTM D4169-05 and ASTM D4169.
- Shipping Conditioning per ASTM D4169-09.
- Accelerated aging conditioning per ISO 11607.
- Particulate release testing per EN 45502-1, EN 455020201 and ISO 14708-3:2008.

In addition to evaluating the general testing, specific components and systems testing is summarized in the following tables.

Model 220P-47 (Posterior) and Model 220A-47E (Anterior) Leads

The MAESTRO leads were assessed for the expected loading and use conditions. The testing that was performed on the leads is summarized in Table 2. Bench testing of the leads and other device components on electromagnetic compatibility (EMC), radio-frequency (RF) wireless technology, and software are summarized Section IX.

Table 2. Model 220P-47 (Posterior) and Model 220A-47E (Anterior) leads bench testing summary

Test	Purpose	Acceptance Criteria	Results
	Legibility of markings.	Lead packaging must remain legible after exposure to cleaning solvents per IEC 60601-1:2012.	PASS
Visual	Test the dimensional specifications for the leads per ISO 5841-3:2000.	Must measure 18.50 ±" in length.	PASS
Inspection	Test the dimensional specifications for the leads connectors per ISO 5841-3:2000.	Must measure 18.50 ±" in length.	PASS
	Test particulate release from the leads per EN 45502-1: 1998, EN 45502- 2-1:2003, and ISO 14708- 3:2008.	Must produce particles counts lower than prespecified criteria, in particles sized as 5, 100, and 1000 µm.	PASS
Composite Tensile Load Testing	Test the tensile strength of lead to anchor per EN 45502-1:1998.	Withstand a pull test (lead to anchor) of 0.5 lbf.	PASS
Following 10 day immersion in 9.0 g/l saline	Test the tensile strength of the suture wing and suture tongue peak removal force per EN 45502-1:1998.	Withstand a pull test of >1.1 N (0.25lb).	PASS
solution at 37°C, leads must remain electrically, mechanically and functionally intact following tensile testing.	Test the composite tensile integrity per ISO 14708-3:2008.	Withstand a pull test of 5N (1.1 lbf) with lead elongation no greater than pre-specified criterion.	PASS
Lead and Connector	Test the ability of the lead body to withstand loading during long term use after conditioning per EN 45502-1.	Withstand flexure cycling (\pm 90 degrees) at a rate of 2 Hz for a minimum of 47,000 cycles, and maintain a DC resistance must be $<$ 30 Ω .	PASS
Flexure Testing	Test the ability of the connector to withstand repeated flexure per EN 45502-1.	Withstand flexure cycling (± 45 degrees) at a rate of 2 Hz for a minimum of 82,000 cycles. DC resistances of the pin to	PASS

Test	Purpose	Acceptance Criteria	Results
		distal electrode, the pin to	
		distal electrode, and ring to	
		ring electrode must meet	
		the pre-specified criteria.	
		Withstand 400,000 cycles	
	Test the ability of the lead	when flexed +/- 60	
	body to withstand cyclical	degrees at central lead	PASS
	fatigue.	body bend radius of 4.76	
Fatigue Testing		mm.	
0 0	Test the ability of the	Withstand minimum	
Leads must	suture wing and tongue to	acceptance criterion of	PASS
remain	withstand tensile force.	0.25N.	
electrically and	Total distribution of the	Withstand a vertical load	
mechanically	Test the ability of the	of 100 g oscillated at 45	PASS
functionally	proximal connector to	degree angle for 82,000	PASS
intact following	withstand cyclical fatigue.	cycles.	
fatigue testing.	Test the ability of the lead	Go gauge can be fully	
	tip to withstand	inserted, with a maximum	
	withdrawal and insertion	insertion and withdrawal	PASS
	forces per ISO 5841-	with less force than the test	
	3:2000.	limit.	
	Test with cyclic		
	polarization for Galvanic	No breakdown in	
	and pitting corrosion of	potential, or signs of	PASS
	the Pt-Ir electrodes per	pitting or corrosion.	
	ASTM F2129-08.		
Corrosion	Test with	The leads must operate	
Resistance	chronopotentiometry for	without corrosion for the	
	Faradaic corrosion of the	stated lifetime under	
	electrodes lead, while	normal operation, and also	PASS
	manually flexing the lead	exceeding maximum pulse	
	at the proximal and distal	amplitude and pulse width	
	junctions.	settings.	
	Test the resistance of the	DC resistance must be	DAGG
T 1 C	pin to distal electrode.	less than 30 Ω .	PASS
Lead Cross	Test the resistance of the	DC resistance must be	DAGG
Circuit DC	ring to ring electrode	less than 30 Ω .	PASS
Resistance	Test the resistance of the	DC resistance must be	D. A. G. G.
	pin to ring electrode	less than 10Ω .	PASS
	Test is to verify that the	After immersion in 9.0	
	device has effective	g/L saline for a minimum	
Distantai Mari	functional electrical	of 10 days at 37°C, the	DAGG
Dielectric Test	insulation between	leakage current between	PASS
	Conductors per EN45502-	all conductors and the	
	2-1:2003.	reference electrode must	

Test	Purpose	Acceptance Criteria	Results
		be less than 2 mA during a	
		voltage application.	

Model 2002 Rechargeable Neuroregulator

Circuit assemblies for the of the Model 2002 Rechargeable Neuroregulator underwent electrical testing after accelerated life test exposure for over 1000 hours of operation at 120°C using MIL-STD 883 Revision G, Test Method Standard, Microcircuits as a guidance. Performance testing included evaluations of electrical safety, functionality (e.g., outputs), mechanical strength, and design validation. Battery testing is summarized in Section IX. Testing of the neuroregulator was performed per applicable regulations and standards including:

- IEC 60601-1:2012
- IEC 60601-1-2: 2001
- EN 60601-1-2: 2007
- ANSI/AAMI/ISO 14708-3:2008
- EN45502-1:1998
- MIL-STD-202G:2002

The testing that was performed on the neuroregulator is summarized in Table 3.

Table 3. Rechargeable Neuroregulator bench testing summary

Test	Purpose	Acceptance Criteria	Results
Visual Inspection	Ensure legibility of markings per EN 45502-1:1998 and ISO 5841-3:2000.	Neuroregulator packaging must remain legible after exposure to cleaning solvents per IEC 60601-1:2005.	PASS
	Test protection of device due to mishandling during the implant procedure by visual	Withstand 70 kPa for 1 hour and 150 kPa for 1 hour.	PASS
	inspection per EN 45502- 1:1998 and EN 5841-3:2000.	Withstand half sine, 500g, 1 ms, 6 shocks, 3 axes.	PASS
		Withstand 3 cycles, 3 hours at -10°C, 3 hours at +55 °C.	PASS
Mass Volume	Test to ensure the volume, mass and physical configuration meet design requirements per EN 45502-1:1998.	Components must comply with requirements for mass and volume, must not have sharp edges, and must meet the prespecified criteria for internal atmosphere.	PASS

Test	Purpose	Acceptance Criteria	Results
Particulate	Test to ensure that final	Component must be	
Release Test	assembly process, and to the	removed from	
	cleaning and packaging	package, and meet	
	processes do not introduce	maximum particulate	PASS
	unacceptable levels of	content after	
	particulates per EN 45502-	immersion in 9.0 g/L	
	1:1998.	saline.	
Dielectric	Testing to verify that the	The leakage current	
Testing	device has effective functional	between all conductors	
	electrical insulation between	and the reference	DAGG
	Conductors per EN45502-2-	electrode must be less	PASS
	1:2003.	than 2 mA during the	
		voltage application.	
Electrical	Test for electrical neutrality	Must not output > 1	
Leakage	per EN 45502-1: 1998.	μA net DC current	
Testing	1	when connected to the	
8		Model 220A/P Leads,	
		Model 2402 Mobile	PASS
		Charger, Model 2403	
		Transmit Coil and	
		nerve equivalent	
		circuit.	
Vibration	Test to validate that the	Withstand 4-400 Hz,	
Testing	neuroregulator remains	$0.7 \text{ (m/s}^2) 2 \text{ Hz}, 30$	PASS
8	electrically and mechanically	minutes, 3 axes.	
	functionally intact following	Withstand 80,000	
	fatigue testing.	cycles when flexed +/-	
		60 degrees at central	PASS
		lead body bend radius	
		of 4.76 mm.	
		Withstand a vertical	
		load of 100 g oscillated	D 1 00
		at 45 degree angle for	PASS
		82,000 cycles.	
		Withstand a	
		displacement of 1 cm	
		over 80,000 cycles.	D 4 6 6
		Extension cycling shall	PASS
		take place at a rate of 2	
		cycles per second.	
		Withstand 80,000 flex	D
		(crush) cycles	PASS
Connector	Test the connector retention	Connector must	
Insertion Limits	after preconditioning in 9.0	withstand straight	PASS
and	g/L saline at room	separating pulls of up	11100
unu	S L saime at 100m	separating puns of up	

Test	Purpose	Acceptance Criteria	Results
Dimensional Requirements	temperature per ISO 14708-1:2000.	to 10 N of force and stay connected to the neuroregulator.	
	Test connector insertion.	The go gauge must be able to be fully inserted; The 2.7 mm gage pin must be inserted to the distance specified using a maximum of 9N of force.	PASS
	Test connector withdrawal.	Disconnects with an insertion force of less than 14 N.	PASS
	Test connector dimensions per ISO 5841-3:2000.	The dimensions of each lead barrel must be in compliance with figure 3 of ISO 5841-3:2000.	PASS
Temperature Rise Test	Test temperature of outer surface when implanted and operated in normal condition per EN 45502-1: 1998.	Outer temperature does not exceed 2°C above normal body temperature.	PASS
	Test comparing the heating effects of two different modes of the Neuroregulator; recharging of the neuroregulator and therapy delivery per EN 45502-1:1998.	Temperature increase measured during charging and therapy delivery is less than 2°C.	PASS
Protection from Damage by External Defibrillators	Test to verify that the Neuroregulator can endure exposure to external defibrillation being applied near an implanted device per EN 45502-1.	Device must pass functional test after testing in conformance to Appendix C.	PASS

Transmit Coils (TCs)

Tensile and flex testing, torsion testing, and dielectric testing depend on the connector and cable and the silicone overmold. Since the connector, cable, and silicone overmold are identical for the Model 2403-60 and 2403-60A Patient Transmit Coils (length, 60 cm) and Model 2403-300 Clinician Transmit Coil (length, 300 cm), performance testing for the Model 2403-60 is representative of testing of all TC Models. Results of bench testing are summarized in Table 4.

Table 4. Model 2403-60 Patient Transmit Coil testing summary

Test	Purpose	Acceptance Criteria	Results
Cable Performance	Test the electrical impedance, and resistance per IEC 60601-1:2005.	Cable must meet prespecified criteria on the frequency of the coil assembly and acceptable impedance value, and withstand 60,000 flexure cycles.	PASS
	Test mechanical performance per ANSI/AAMI/EC53:1995 (R2008).	Must withstand tensile, flexure, and torsion testing after 90,000 cycles and rotation from 0 to ±90 degrees.	PASS
	Test dielectric withstand of cable with antenna and LEMO connector per ANSI/AAMI/EC53:1995 (R2008).	Withstand preconditioning in a humidified environment of 93% ±3% at 32°C, followed by immersion in 9.0 g/L saline, flex testing, and rotation cycles without cable failure. Leakage must not exceed 1 µA.	PASS
Tensile Strength of Antenna and Connector	Test tensile strength of cable (LEMO) connector and antenna per ANSI/AAMI/EC53:1995 (R2008).	Antenna tensile strength must be equivalent or better than 32.8 lbf, and withstand torsion LEMO torsion flexion of 30,000 cycles without loss of conductivity.	PASS
General Electrical Safety Testing	Test to verify that the MC meets international standards for electrical safety per 60601-1:2012.	Meets the requirements for dielectric withstand	PASS

<u>Model 2402 Mobile Charger</u> Testing for the Model 2402 Mobile Charger is summarized in Table 5.

Table 5. Model 2402 Mobile Charger testing summary

Test	Purpose	Acceptance Criteria	Results
Sales Package High Humidity Storage Test	Test to verify that the sales package can endure high humidity storage conditions without deterioration.	Meets the requirements of EN 45502-1:1998 Section 10.2	PASS
Temperature Elevation of the MC Surface	Test to verify that the surface temperature does not exceed temperature	The MC, when provided with a representative load by the Model 2403-60	PASS

limits per IEC 60601- 1:2012. MAESTRO Model 2002 Neuroregulator, must meet the pre-specified temperature criterion stated in IEC 60601-1. Test to verify that that the rigidity of the MC enclosure provides an adequate level of protection from internal damage from application of force, impact from transmit coil and MAESTRO Model 2002 Neuroregulator, must meet the pre-specified temperature criterion stated in IEC 60601-1. The MC enclosure, when subjected to the rigidity, must be sufficient to prevent an inward directed force from appreciably damaging the enclosure or	S
Neuroregulator, must meet the pre-specified temperature criterion stated in IEC 60601-1. Test to verify that that the rigidity of the MC enclosure provides an adequate level of protection from internal damage from application Neuroregulator, must meet the pre-specified temperature criterion stated in IEC 60601-1. The MC enclosure, when subjected to the rigidity, must be sufficient to prevent an inward directed force from appreciably PAS	S
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Enclosure Rigidity Test protection from internal damage from application prevent an inward directed force from appreciably PAS	S
Rigidity Test damage from application force from appreciably PAS	S
Rigidity Test damage from application force from appreciably PAS	S
RIGINITY LAST	
misuse per IEC reducing creepage	
60601:1990, Clause 21 distances and air	
and 60601-1:2005, Clause clearance.	
15.3.2.	
Isolation Test to verify that the Isolation is sufficient to PAS	S
between electrical isolation prevent accidental	
Clinician between the Clinician coupling of mains	
Programmer Programmer port and the terminal voltage to the	
Port and Transmit Coil connector transmit coil in the event	
Transmit Coil per IEC 60601:2005. of a malfunction of the	
Connector Programmer's USB port.	
Immunity to Test to verify that the Mobile Charger must PAS	S
Electrostatic electrical isolation sustain electrostatic	
Discharge between the Clinician discharges without any	
Programmer port and the failures or changes in	
Transmit Coil connector functionality.	
per IEC 60601:2005.	
Electrical Test to verify that the MC Meets the requirements PAS	S
Safety Testing meets international for electrical isolation	
standards as set forth in between the clinician	
EN 45502-1:1998, ISO programmer port and	
6060101:1990, ISO transmit coil connector,	
606010101:2005, ISO immunity from electrical	
6060102:2001, ISO discharge, and produce	
61000-4-2:2009, and ISO $\leq 1 \mu A$ under dielectric	
8601:2004 strength testing.	

Electromagnetic compatibility (EMC), electromagnetic interference (EMI), and radio-frequency (RF) wireless testing.

The MAESTRO System was tested for EMC, EMI, and RF wireless performance. Results are summarized in Table 3. Testing was performed in accordance with applicable standards, including:

- IEC 60601-1-2 3rd Edition
- IEC 61000-4-2
- IEC 61000-4-3
- IEC 61000-4-4
- IEC 61000-4-5
- IEC 61000-4-6
- IEC 61000-4-8
- IEC 61000-4-11
- EN 45502-1
- ISO 14708-3:2002
- EN45502-1:1997
- EN 300 330-2 V1.3.1
- EN 55011:2007
- FCC Part 18 Subpart C
- FCC Part 15 Subpart C

Table 6 summarizes the EMC, EMI, and wireless technology testing and results.

Table 6. Testing for electromagnetic compatibility, electromagnetic interference and radio-frequency wireless technology

Test	Purpose	Acceptance Criteria	Results
Immunity Testing fields	Test for protection from static magnetic per ISO 14708-3.	Neuroregulator and leads operate normally when exposed to 1 mT and 50 mT, meeting A-line and B-line criteria.	PASS
	Test for protection from magnetic fields in the range 10 Hz to 30 MHz per ISO 14708-3.	Neuroregulator and leads operate normally, with no loss of function when tested for performance criterion A of performance criterion B.	PASS
	Test for protection from electromagnetic fields in the range of 30 MHz to 450 MHz, and electromagnetic fields in the range of 450 MHz to 3 GHz.	System operates normally, with no loss of function when tested for performance criterion A of performance criterion B.	PASS
High Power Electrical Fields Exposure	Test to verify that the Neuroregulator can endure exposure to high powered electrical fields without harming the device per EN 45502-1.	Neuroregulator, Transmit Coil and Mobile charger must meet functional test criteria per Annex D after exposure.	PASS

Test	Purpose	Acceptance Criteria	Results
Protection from Electromagnetic Non-ionizing Radiation	Test for protection of the MAESTRO System to magnetic fields in the range of 30 Hz-30 MHz per 45502-2-1:1997	Neuroregulator and leads operate with continuous therapy as intended, within pre-specified limits with no loss of function	PASS
Protection from Electromagnetic Fields	Test for conducted and radiated emission testing per EN 60601-1-2:2007, EN 55011:2009 and FCC Part 15 Subpart B.	Neuroregulator and leads operate as intended, within pre-specified limits with no loss of function.	PASS
Protection from Electromagnetic Fields	Test for immunity from electrostatic discharge, radiated fields, fast/transient bursts, surge transients, conducted disturbance, power frequency magnetic field, voltage dips/interruptions/variations, and transients and surges per EN60601-1-2:2007, EN 61000-4-2:2009, EN 61000-4-3:2006, EN 61000-4-5:2006, EN 61000-4-5:2006, EN 61000-4-5:2006, EN 61000-4-11:2004, ETSI EN 301-489-3, ISO 7636-2:2004, FCC Part 15 Subparts B and C, FCC Part 18 Subpart B.	Neuroregulator, transmit coil, anterior and posterior leads, mobile charger, programmer cable, clinician programmer and AC recharger operate as intended in the electromagnetic fields for the pre-specified frequency and power ranges, loads and burst conditions.	PASS

Software

The software for the MAESTRO system components was determined to have a MAJOR level of concern. The software for the Model 2502 Clinician Programmer, Model 2402 Mobile Charger, Model 2002 Neuroregulator, and Operating Systems were evaluated through verification and validation testing to confirm that it met user needs and performed as intended. Software testing demonstrates conformance to the following standards and guidances:

- ISO 13485:2003
- 90/385/EEC:1990 (Amended 2007/47/EC)
- ISO/IEC 14971:2007
- EN 45502-1:1998
- IEC 60601-1:2005 (3rd Edition)

- IEC 60601-1-4:2005 (Amendment 1, 2nd Edition)
- IEC 62304:2006
- IEEE Standards Collection for Software Engineering: 1999
- FDA Guidance, "Guidance for Industry, FDA Reviewers and Compliance on Off-The-Shelf Software Use in Medical Devices," 1999
- FDA Guidance, "General Principles of Software Validation; Final Guidance for Industry and FDA Staff," 2002
- FDA Guidance "Guidance for Industry Cybersecurity for Networked Medical Devices Containing Off-The-Shelf (OTS) Software," 2005

B. Animal Studies

In Vivo Animal Studies

EnteroMedics evaluated the safety of implantation and nerve blockade of the porcine abdominal vagus nerve trunk. The device was tested using a variety of device components. An earlier design of the neuroregulator (Radiofrequency 2, or RF2) was tested with a 100% platinum electrode Model 1200 electrode. The tested device was revised to include an RF2 neuroregulator for use with a Model 2200 platinumiridium electrode. With iterations in device design, device components representing the test articles used in clinical study were tested, including testing of the Rechargeable neuroregulator in combination with the Model 2200 electrode. For the stimulation algorithm, pulse frequency was always maintained at 5000 Hz, and the duty cycle was always set to deliver 5 minutes of VBLOC therapy ON, followed by 5 minutes of VBLOC therapy OFF.

Table 7. Summary of porcine studies conducted on VBLOC therapy

Animal Study	Model RNR + Leads	Study Duration	Therapy Algorithm: Current, Pulse Width,
ID			VBLOC
TR01	#1000 RNR; #1200 leads	1-3 weeks	2-4mA, 100μS, 12 hrs./day
TR02	#1000 RNR; #1200 leads	4 weeks	2-6mA, 100μS, 12 hrs./day
TR03	#1000 RNR; #1200 leads	8 weeks	2-6mA, 100µS, 12 hrs./day
TR04	#1000 RNR; #1200 leads	12 weeks	4-6mA, 100μS, 12 hrs./day
TR05	#1000 RNR; #1200 leads	1-3 weeks	6mA, 100µS, 12 hrs./day
TR06	#1000 RNR; #1200 leads	12 weeks	6mA, 100µS, 12 or 24
			hrs./day
TR07	#1002 RNR; #2200 leads	9 days	6mA, 90µS, 24 hrs./day
TR08	#1002 RNR; #2200 leads	4-12 weeks	6mA, 90µS, 24 hrs./day
TR09	#1002 RNR; #2200 leads	12 weeks	6mA, 90µS, 24 hrs./day
TR10	#1002 RNR; #2200 leads	4 weeks	8mA, 90µS, 24 hrs./day
TR11	#2002 RNR; #2200 leads	4 weeks	6mA, 90µS, 24 hrs./day
TR12	#2002 RNR; #2200 leads	12 weeks	8mA, 90µS, 24 hrs./day

Analysis

Device components that are designed to be internally implanted in patients include the neuroregulator and leads. For the animal studies, the neuroregulator and leads were exteriorized due to the anatomical limitations of using the porcine animal model. Exteriorization of these device components, and the natural growth of the animal subjects, resulted in chronic pulling forces that resulted in trauma to the nerve. Exteriorization of the neuroregulator and leads was reported to produce neural trauma which likely exacerbated the neurodegeneration observed in histological sections of the implanted nerves. Therefore, the data provided by EMI may not have been representative of the long term safety of device implantation in humans. Results supported device development, and confirmed that gastric contraction function was preserved with VBLOC therapy.

C. Additional Studies

Additional performance studies are briefly described in Table 8.

Table 8. Miscellaneous performance studies on the MAESTRO Rechargeable System

Test	Purpose	Acceptance Criteria	Results
Battery Testing	with relation to capacity, over-charging per IEC	Batteries withstood an internal short circuit (nail test, n=14), external short circuit (n=8) and over-charging (n=3) without exhibiting adverse chemical/thermal reaction.	PASS
Suture Needle Fit Test	adequately shaped to accommodate a range of suture needle sizes.	Each suture needle must pass freely through each of the 3 suture holes provided on the device.	PASS
Sterilization of the Neuroregulator, Leads, and Torque Wrench	bioburden, endotoxin, and ethylene oxide residual levels per ANSI/AAMI/ ISO 11737-2:2009, ISO 11135:2014: Annex E, ANSI/AAMI/ISO 10993- 7:2008, ISO 11737-	Sterilization must demonstrate per a sterility assurance of at least 10 ⁻⁶ . Endotoxin levels must not have more than 20 Endotoxin Units (EU/)/device for the summation of the blood-contacting devices, and meet test criteria for bioburden and colony forming units. Ethylene oxide residuals must not exceed test criteria.	PASS

Test	Purpose	Acceptance Criteria	Results
	Suitability (Bacteriostasis/ Fungistasis) Te20).st, and U.S. Pharmaceutical Convention <85>.		
Packaging	Testing to ensure that the sterile integrity and physical properties of packaging meets shelf-life criteria per ASTM F1980-07:2011.	Packages tested met the acceptance criteria for seal strength and dye penetration to demonstrate a 3-year shelf life for the leads, 18-month shelf-life for the torque wrench and neuroregulator. Conditioning and test samples are used to evaluate each step in the packaging process.	PASS
	Testing of the Patient Transmit Coil as an externally patient contacting device with limited duration of exposure (≤ 24 hours) to ensure conformance to ISO-10993-1:2009, ISO- 10993-2:2006, and ISO- 10993-5:2009.	Must meet pre-specified criteria for cytotoxicity, irritation. and sensitization.	PASS
Biocompatibility	Testing of the of the neuroregulator and leads as permanent, tissue contacting, implanted device components to ensure conformance to ISO-10993-1:2009, ISO-10993-2:2006, ISO	Must meet pre-specified criteria for genotoxicity, mutagenicity, cytotoxicity, irritation, sensitization, implantation, acute systemic toxicity, and systemic toxicity, and demonstrate non-significant levels of risk with respect to leachables and extractables.	PASS

X. SUMMARY OF PRIMARY CLINICAL STUDIES

Overview

Three (3) studies (one (1) pilot and two (2) pivotal studies) were conducted. The primary effectiveness for each of the studies was to demonstrate a significantly greater percentage of weight loss at the 12 month time point, with a super-superiority margin of 10%. For the two (2) pivotal studies, which utilized a randomized, double blind approach, super-superiority was determined by comparing the percent excess weight loss (%EWL) at the 12 month time point in VBLOC treatment versus Control arms. For the pilot study, which utilized an open label approach, super-superiority was determined

by comparing the %EWL at baseline versus the %EWL at the 12 month time point. Although super-superiority was not demonstrated in any of the three (3) clinical trials, a statistically significant difference between the VBLOC therapy arm and the Sham control arm was observed. All three (3) studies met the safety endpoint, which was to show a serious adverse event (SAE) rate of \leq 15%.

EMPOWER Pivotal Study

The first pivotal study to be conducted in the U.S. was entitled the EMPOWER Clinical Trial. The trial was initiated in 2007 and featured the MAESTRO RF2 system. Device components included the Model 1002 Neuroregulator, Model 2200 Leads, Model 104 Controller, Model 1403 Transmit Coil and accessories, Model 2500 Programmer Software, and Model P00062-000 Battery Charger. The transmit coil belt was worn "fanny pack" style to optimally align the coil to provide power to the RNR. EMPOWER was designed as a prospective, randomized (2:1), double-blind, controlled trial with evaluation of primary endpoints at 12 months. The intended patient population was those who have a BMI >40 kg/m² to 45 kg/m², or \geq 35 to 39.9 kg/m² with obesity related comorbidities. A total of 294 subjects were randomized to either VBLOC (192 subjects) or sham therapy (102 subjects) at 15 institutions. For the sham therapy, the Sham patients received the implantable device components as well as lead impedance and safety checks, but the therapy algorithm was set to deliver 0 mA of VBLOC therapy.

There were 294 subjects implanted and randomized, including 192 VBLOC (treatment) and 102 Sham control subjects. At the 12 month time point, there were 22 SAEs (11.5%) in the VBLOC treatment arm, of which 22 (4.7%) were related to either implant/revision procedure, therapy, or the device. In the Sham control arm, there were 11 SAEs (10.8%) of which 8 (7.8%) were related to either implant/revision procedure, therapy, or the device. Table 9 presents longer term data on the most frequent types of adverse events through 48 months that were related to either implant/revision procedure, therapy, or the device.

Table 9. EMPOWER Study: Most frequent (≥5%) implant/revision procedure, therapy, or device-related adverse events through 48 months.

Event Type	Treatment Group (n=192)	Sham Control (n=102)
	Number (%)	Number (%)
Pain, neuroregulator site	56 (29.2%)	31 (30.4%)
Heartburn/dyspepsia	46 (24.0%)	17 (16.7%)
Pain, other	35 (18.2%)	12 (11.8%)
Other	36 (18.8%)	17 (16.7%)
Pain, abdominal	33 (17.2%)	20 (19.6%)
Nausea	23 (12.0%)	8 (7.8%)
Skin reaction to coil/coil adhesion method	21 (10.9%)	13 (12.7%)
Belching	19 (9.9%)	12 (11.8%)
Constipation	19 (9.9%)	10 (9.8%)

Event Type	Treatment Group (n=192)	Sham Control (n=102)	
	Number (%)	Number (%)	
Chest pain	17 (8.9%)	3 (2.9%)	
Wound redness	13 (6.8%)	4 (3.9%)	
Diarrhea	9 (4.7%)	8 (7.8%)	
Bloating, abdominal	9 (4.7%)	7 (6.9%)	
Incision pain/incision site	8 (4.2%)	8 (7.8%)	
Neuroregulator malfunction	4 (2.1%)	7 (6.9%)	

The primary effectiveness endpoint was to demonstrate a significantly greater percentage of excess weight loss (% EWL, MetLife method, with a 10% supersuperiority margin) with subjects in the active VBLOC arm after 12 months of VBLOC Therapy when compared to sham control subjects. This objective was not met, since the mean %EWL in the VBLOC treatment and sham control arms was 12.1 ± 17.5 and 12.0 ± 20.8 , respectively. EnteroMedics has suggested that the requirement for patients to wear the transit coil and controller for several hours per day in order ensure delivery of VBLOC therapy could have led to the lack of compliance with recharging instructions and thus contributed to the lack of effectiveness findings.

The primary safety objective was to demonstrate that the long term (through 12 months), implant/revision procedure, device, and therapy related serious adverse event (SAE) rate is less than 15%. The safety objective was met, since the rate for these SAEs was 5.2% in the treatment arm and 2.9% in the control arm. There were no deaths or unanticipated adverse events (UAEs) observed.

VBLOC DM2 Pilot Study

VBLOC-DM2 was a pilot trial of the MAESTRO[®] Rechargeable System performed on obese subjects with Type 2 Diabetes. It was designed as an open label, single-arm, multi-center trial conducted on 28 subjects at five (5) centers outside the U.S. All subjects received all implantable components of the MAESTRO[®] Rechargeable System at the time of implantation.

Mean weight loss of 24% EWL was reported at 12 months. There have been no deaths or unanticipated adverse events (UADEs); however, four (4) device or implant-related SAEs have been reported through 36 months. Table 10 lists AEs related to device or procedure that occurred in greater than 5% of Type 2 Diabetic subjects.

Table 10. VBLOC-DM2: Adverse Events Related to Device or Implant/Revision Procedure

AE Type	N patients (%)	N events
Heartburn	8 (28.6%)	8
Constipation	6 (21.4%)	7
Other	4 (14.3%)	6
Pain (neuroregulator site)	5 (17.9%)	6
Nausea	3 (10.7%)	5
Pain	3 (10.7%)	4
Abdominal pain	2 (7.1%)	3
Abdominal cramps	2 (7.1%)	2
Chest pain	2 (7.1%)	2
Wound redness or irritation, neuroregulator site	2 (7.1%)	2
Wound redness or irritation, trocar site	2 (7.1%)	2

RECHARGE Pivotal Study

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of abdominal vagus nerve blocking therapy with the Maestro[®] Rechargeable System for use in weight reduction in patients aged 18 years through adulthood who have a Body Mass Index (BMI) of 40 to 45 kg/m², or a BMI of ≥35 to 39.9 kg/m² with one or more obesity related co-morbid conditions, and have failed at least one supervised weight management program within the past five (5) years in the U.S. and Australia under Investigational Device Exemption (IDE) # G070025. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below. Approval for the study was granted in March 2011. Subjects were implanted with the MAESTRO System between May 2011 and December 2011.

A. Study Design

Patients were treated between May 2011 and January 2013. The database for this PMA reflected data collected through May 2013 and included 239 patients. There were 10 investigational sites (8 in the U.S. and 2 in Australia). This study was a prospective, randomized, double blind, parallel-group, multi-center trial to evaluate the safety and efficacy of the device in treating obesity with 12-month follow-up in 239 randomized patients. The intended patient population was those who had a BMI 40-45 kg/m² or 35-39.9 kg/m² with obesity related comorbidities. The subjects were randomized 2:1 to either VBLOC therapy or a Sham Control Group. Post-implant follow-up visits were scheduled at weeks 1-4, 6, 8 and 10, and then monthly from months 3-12. Longer term follow-up was scheduled out to 5 years post-implant. Subjects were blinded to the assigned treatment group and unblinding of subjects

began once all subjects had completed the month 12 evaluation.

Subjects in the Control Group (sham) were implanted with a nonfunctional neuroregulator device and no leads were implanted. These subjects received a sham surgical procedure, which involved placing approximately the same number of incisions (3-5) and utilized general laparoscopic techniques. The nonfunctional neuroregulator operates in the same manner as the functional neuroregulator, but did deliver electrical stimulation. The neuroregulator's lead sockets were filled with medical grade silicone adhesive to ensure that no electrical current was delivered by the device. As with the active functional neuroregulator, the sham nonfunctional neuroregulator contains a battery and thus required recharging. The battery in the sham device becomes depleted and interacts with the programmer in the same fashion as the active device. All subjects remained blinded through at least the 12 month follow-up visit, after which the Sham subjects who chose to continue in the trial had the option of having the MAESTRO® Rechargeable System fully implanted, and receiving active therapy.

A blinded Clinical Event Committee (CEC) reviewed and adjudicated all serious adverse events (SAEs). A blinded Data and Safety Monitoring Board (DSMB) reviewed the trial on an ongoing basis. The DSMB reviewed aggregated clinical laboratory and electrocardiographic data and concluded that there were no findings of clinical significance or concern. No changes in intra-cardiac conduction (PR interval, QRS duration), ventricular repolarization (QTcF interval), or ventricular arrhythmias were associated with either the treatment or control groups in the study.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the ReCharge Study was limited to patients who met the following inclusion criteria:

- Informed consent.
- Body mass index (BMI) ≥ 40 kg/m² to 45 kg/m² or BMI ≥ 35 kg/m² to kg/m² with at least one (1) obesity related co-morbid condition. Co-morbid conditions may include one or more of the following and will be documented on the appropriate case report form:
 - Type 2 diabetes mellitus as defined in the 5th inclusion criteria (limited to 10% of randomized subjects)
 - o Hypertension as defined by systolic pressure ≥140 mmHg and/or diastolic pressure ≥90 mmHg
 - o Treated or untreated hypertension with systolic ≥140 mmHg and/or diastolic ≥90 mmHg
 - Treated hypertension with systolic <140 mmHg and/or diastolic <90 mmHg
 - o Dyslipidemia as defined by total cholesterol ≥200 or LDL ≥130

- Treated or untreated dyslipidemia with total cholesterol ≥200 or LDL ≥130
- o Treated dyslipidemia with total cholesterol <200 or LDL <130
- o Sleep apnea syndrome (confirmed by overnight p02 studies)
- o Obesity-related cardiomyopathy
- Females or males.

Note: females of child-bearing potential must have a negative urine pregnancy test at Screen and also within 14 days of implant procedure followed by physician-approved contraceptive regimen for the duration of the study period.

- 18-65 years of age inclusive.
- Type 2 diabetes mellitus subjects with:
 - O Glycosylated hemoglobin (HbA1c) 7.0-10% inclusive at screening visit (Undiagnosed subjects that are found to have a HbA1c 7-10% at screening must see their primary physician for diagnosis and medical treatment before continuing in trial),
 - o Onset of Type 2 diabetes mellitus: 12 years or less since initial diagnosis,
 - Currently not using insulin therapy, GLP-1 receptor agonists (e.g., exenatide), for diabetes treatment and have not been on these treatments in the past 6 months, and
 - o Serum creatinine within normal reference range:
 - No history of proliferative retinopathy
 - No history peripheral neuropathy
 - No history of autonomic neuropathy
 - No history of coronary artery disease, with or without angina pectoris
 - No history of peripheral vascular disease
- Failure to respond to a supervised diet/exercise programs in which the subject was engaged within the last five (5) years.
- Ability to complete all study visits and procedures.

Patients were <u>not</u> permitted to enroll in the ReCharge Study if they met any of the following exclusion criteria:

- Concurrent chronic pancreatic disease.
- History of Crohn's disease and/or ulcerative colitis.

- History of bariatric surgery, fundoplication, gastric resection or major upperabdominal surgery (acceptable surgeries include cholecystectomy, hysterectomy)
- History of pulmonary embolism or blood coagulation disorders.
- Clinically significant hiatal hernias (>5cm) known from subject's medical record or determined by barium swallow (upper GI x-ray) or upper endoscopy per PI discretion prior to implant.
- Current cirrhosis, portal hypertension, and/or esophageal varices.
- Intra-operative exclusion: hiatal hernia requiring surgical repair or extensive dissection at esophagogastric junction at time of surgery.
- Treatment with prescription weight-loss drug therapy within the prior three (3) months and the use of prescription drug therapy or the use of over-the-counter weight loss preparations for the duration of the trial.
- Smoking cessation within the prior six (6) months.
- Known genetic cause of obesity (e.g., Prader-Willi Syndrome).
 - Weight loss of more than 10% of body weight in the previous 12 months.
- Physician-prescribed pre-operative weight loss program prior to surgery.
 Note: Study subject may continue any personal eating plan they were on prior to study enrollment.
- Current Type 1 diabetes mellitus (DM).
- Current or recent history (within 12 months) of ongoing bulimia.
- Current alterations in treatment for thyroid disorders (stable treatment regimen for prior three (3) months acceptable).
- Current alterations in treatment for epilepsy (stable treatment regimen for prior six (6) months acceptable).
- Current treatment for peptic ulcer disease (previous history acceptable).
- Chronic treatment (more than four (4) weeks of daily use) with narcotic analgesic drug regimens (treatment with non-steroidal anti-inflammatory drugs is acceptable).

- Current alterations in treatment regimens of anti-cholinergic drugs, including tricyclic antidepressants (stable treatment regimen for prior six (6) months is acceptable).
- Current medical condition that, in the opinion of the investigator, would
 make subject unfit for surgery under general anesthesia or that would be
 exacerbated by intentional weight loss. Some examples include diagnosis of
 cancer, recent heart attack, recent stroke, or recent serious trauma.
- Presence of permanently implanted electrical powered medical device or implanted gastrointestinal device or prosthesis (e.g., pacemakers, implanted defibrillators, neurostimulators etc.).
- Planned or contemplated use of Magnetic Resonance Imaging (MRI) or oncologic radiation during the course of the trial.
- Psychiatric disorders (including untreated severe depression, schizophrenia, substance abuse, bulimia nervosa, etc.) or limited intellectual functioning which would potentially compromise the participant's ability to fully comprehend and/or cooperate with the study protocol. Psychiatric disorders will be established by a review of subject's medical history. For depression, a Beck Depression Inventory (BDI) score ≥ 29 will be considered to indicate severe depression.
- Current, active member of an organized weight loss program (e.g., Weight Watchers, Take Off Pounds Sensibly (TOPS)).
- Current participant in another weight loss study or other clinical trials.
- Have a friend or family member who is currently participating or is planning to participate in this clinical trial.
- Patient reported:
 - o inability to walk for about 10 minutes without stopping
 - o feeling of pain in chest when doing physical activity
 - o feeling of pain in chest when not doing physical activity
- Clinically significant cardiac rhythm disorder that requires either medical and/or surgical intervention (e.g., paroxysmal or chronic atrial fibrillation).

2. Follow-up Schedule

Weight Management Counseling

All subjects were required to participate in a weight management program,

consisting of recommendations regarding diet, exercise, and behavior modification throughout the study. All subjects were taught the same basic information about weight loss and physical activity and were given the opportunity to practice related behavioral skills both during educational sessions and at home. Modifications to their current diet and exercise plan were taught by a trained adviser through seventeen (17) individual sessions during the first year along with the regularly scheduled trial visits. The subjects were required to complete a 7 day diet and exercise diary prior to the implant, weeks one (1) through four, and once per month during the first year of the study. Following the first year, group sessions were scheduled for the duration of the study. Subjects were required to cover the elements of the curriculum in a minimum 17 individual face-to-face sessions during the first 12 months after initiation in order to complete the year one behavioral weight loss instruction.

Therapy Algorithms (Device Settings)

The VBLOC treatment group neuroregulators were initially set to deliver current amplitude of 1 mA with a treatment schedule of 13 hours per day. The amplitude was increased to 3 mA at the week 1 visit, and increased by 1 mA each following week reaching 6 mA at week 4. The programming sessions and the systematic amplitude increases were performed for both VBLOC and Sham groups to maintain blinding. Subjects who could not tolerate 3 mA at week 1 or 1 mA incremental increases were increased at a slower rate and/or smaller increments. Other therapy parameters included a ramp-up time of 0 to 50 seconds, an ON time of 2 to 5 minutes, and an OFF time of 5 to 10 minutes. Therapy at 6 mA (or the maximal tolerated amplitude) and a 13 hour delivery schedule per day were then maintained for the remainder of the first 6 months. At month 6, the goal was for subjects to achieve a 15% EWL. Any subjects reporting unacceptable adverse events that were possibly related to therapy underwent modifications of the device parameters including a decrease in amplitude, an increase in the OFF Time, an increase or decrease ramp-up time, or an adjustment in the daily treatment schedule.

Beyond the six (6) month visit, the therapy settings were left unchanged if the subject was losing weight and was not experiencing unacceptable adverse events. At the 6, 7, 8, 9, 10, and 11 month visits, the subjects had their % EWL from implant compared with the expected rate of 2.5% EWL per month. If the subject was either not losing weight at an expected rate or was experiencing unacceptable adverse events, the therapy settings were adjusted up or down. If a subject lost more than 2.5% EWL, no changes were made in the settings. Subjects that achieved the monthly %EWL but gained weight from the previous month had further adjustments in the therapy parameters. The maximum amplitude setting was 8.0 mA, and the maximum daily hours of VBLOC therapy was 18 hours.

Scheduled visits

Table 11 summarizes the scheduled visits and patient assessments. Adverse

events and complications were recorded at all visits.

Table 11. Schedule of trial events: Screening through 12 month follow-up

Screening [Enrollment]	Randomization/ Implant/Initiation	week 1 Visit 7 ±3 days after Implant	Follow-up Visits 2, 3, 4, 6, 8, 10, 12 weeks (±3 days); 4, 5, 6, 7, 8, 9, 10, 11, 12 months (±14 days) after randomization
 Informed consent Inclusion/exclusion criteria assessments Body weight Body height Vital signs* Medication use assessment Psychological assessment Waist and hip circumferences Clinical laboratory assessments Subject Questionnaires Physical exam 7 day diet and activity diary 12 lead ECG Preoperative assessments (upper GI x-ray or upper endoscopy) Device overview and training 	 Body weight Vital signs Adverse event/medication use assessment Randomized to treatment groups Device implant (after all procedures above) 	 Subject self-assessment (optional) Body weight Vital signs Adverse event / medication use assessment Device training 7 day diet and activity diary Blinding status Weight management begins 	 Subject self-assessment (optional) Body weight Vital signs* Adverse event/ medication use assessment Physical exam if needed Clinical laboratory assessments (6 & 12 months) Waist and hip circumferences (12 months) Weight management Device interrogation Current amplitude adjustments as indicated Assess/maximize compliance with recharging 12 lead ECG (4, 8, 12 months) 7 day diet and activity diary Blinding status (6 & 12 mo.) Subject Questionnaires (3, 6 & 12 mo.) Telephone contact with subject between visits (12 week- 6 months)

^{*}Blood pressure collected in triplicate at screening, implant, and months 3, 6, 9, and 12 month visits.

3. Clinical Endpoints

With regards to safety, the primary safety endpoint of the ReCharge trial was to demonstrate that the 12-month serious adverse event (SAE) rate related to implant or revision procedures, device, or therapy was less than a performance goal of 15% among the subjects in the VBLOC group.

With regards to effectiveness, there were two (2) co-primary effectiveness endpoints. The first co-primary effectiveness endpoint was percent excess weight loss (%EWL) at 12 months after randomization with ideal body weight calculated using the BMI method (i.e., the weight a subject would have with a BMI of 25 kg/m²). The objective of the analysis was to show that the mean %EWL in the VBLOC group is 10% greater than the %EWL in the control Sham group. The super-superiority margin of 10% was thought to represent a clinically meaningful difference between active VBLOC therapy and a Sham control. For each subject, the %EWL is the weight lost between baseline and 12 months divided by the subject's excess weight, where excess weight is the difference between baseline weight and ideal body weight.

The analysis of %EWL was based on a t-test with a one-sided significance level of 2.5%. The primary analysis of this endpoint was based on the intent-to-treat group consisting of all randomized subjects. Note that not all subjects had a weight available at 12 months. For these subjects, their last available weight was used in place of the missing month 12 weight.

The second co-primary effectiveness endpoint was based on responder rates with the following two requirements: (i) at least 55% of VBLOC subjects would achieve a %EWL of at least 20%; and (ii) at least 45% of VBLOC subjects would achieve a %EWL of at least 25%.

With regard to success/failure criteria, the assessments of these objectives were based on observed rates rather than statistical hypothesis tests and according to the protocol both of these objectives should be met for trial success.

B. Accountability of PMA Cohort

At the time of database lock, of 239 subjects enrolled in the PMA study, there were 162 subjects randomized to the VBLOC group and 77 subjects randomized to the Sham control group. However, only 233 subjects were implanted: Five (5) VBLOC subjects failed to get the fully-implanted device due to intra-operative exclusions and one (1) Sham control subject withdrew from the trial prior to the scheduled procedure time. Through the 12 month time point, the reasons given for subject withdrawal in the VBLOC treatment arm included three (3) intra-operative exclusions, 1 comorbid condition, and 1 surgeon discretion. "Subject decision" was the reason given for the subject who withdrew from the Sham control arm. Ninety-one percent (91%, n=147) of the randomized VBLOC and 86% (n=66) of the

randomized Sham subjects are available for analysis at the completion of the study, the 12 months post-operative visit (Figure 2). The combined number of VBLOC plus Sham subjects available at 12 months was eighty-nine percent (89%). At 18 months, the follow-up rate was 72% (n=117) in the VBLOC group and 55% (n=42) in the Sham control group.

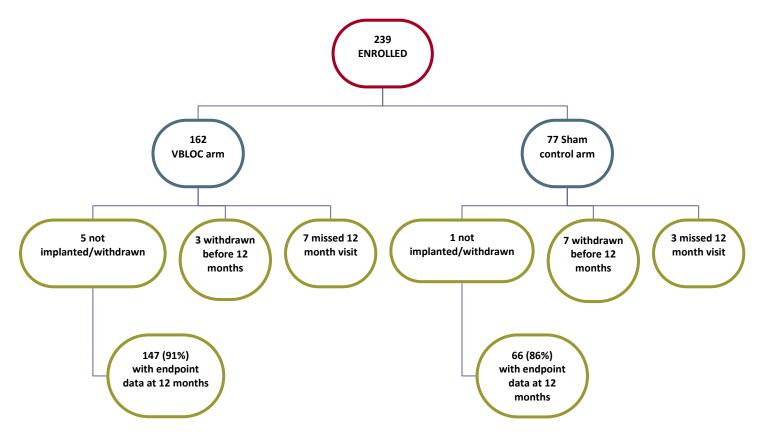


Figure 2. ReCharge subject accountability

C. Study Population Demographics and Baseline Parameters

Table 12 lists the baseline demographics of the Recharge study population of subjects enrolled in the U.S. During the June 17, 2014 Advisory Meeting, the Panel members commented that the majority of U.S. subjects were female and Caucasian.

The trial included 239 randomized subjects (162 VBLOC and 77 Sham) at 10 investigational sites (8 in the U.S. and 2 in Australia). Of the 239 randomized subjects, 233 received an implanted device (157 VBLOC, 76 Sham). Among the randomized subjects, 84.9% (141 VBLOC and 62 Sham) of the subjects were female, 92.9% (149 VBLOC and 73 Sham) were Caucasian, the average age was 47 years (range: 18-65), average BMI at implant was 40.9 kg/m² (range: 34.4-48.4), and 6.3% (9 VBLOC, 6 Sham Control) had type 2 diabetes mellitus. No significant differences were found between the VBLOC and sham groups for any of the recorded demographic and baseline variables.

Table 12. Baseline Demographics and Health Characteristics of Recharge Subjects

Characteristic		VBLOC (n=162)	Sham (n=77)	P-value
Gender	Female	87.0%	80.5%	0.245
	Male	13.0%	19.5%	
Age (years) at screening		47.1±10.3	46.6±9.4	0.693*
Race	Caucasian	92.0%	94.8%	0.592
	African American	4.9%	3.9%	1.000
	Native American	1.2%	1.3%	1.000
	Asian	0.6%	1 (1.3%)	0.541
	Hawaiian/Pacific Islander	0.6%	0%	1.000
Height (m)		1.7±0.1	1.7±0.1	0.112*
BMI (kg/m ² , at implant)		40.9±2.8	40.9±3.1	0.969*
Weight at implant (kg)		11216±11.8	123.0±11.3	0.117
Excess weight (kg) at implant		43.7±8.7	44.9±9.5	0.371
Waist circumference (cm) at screening		121.1±11.8	123.0±11.3	0.236
Type 2 diabetes mellitus		9 (5.6%)	6 (7.8%)	0.571
Hypertension		63 (38.9%)	32 (41.6%)	0.920
Dyslipidemia		91 (56.2%)	46 (59.7%)	0.884
Obstructive Sleep Apnea		33 (20.4%)	23 (29.9%)	0.267

Note: Data are presented as mean \pm SD for continuous variables. Data are presented as n (%) for categorical variables. P-values for continuous variables were calculated using a Student's t-test (no asterisk) or a Wilcoxon rank sum test (*) if the variable was not normally distributed based on the Shapiro-Wilk normality test. Categorical variables were compared using Fisher's exact test.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the adverse event rates in the cohort of patients available for the 12 month evaluation. The key safety outcomes for this study are presented below. Adverse events are reported in Tables 13 thru 15.

Serious Adverse Events in the Randomized Population

Among the 162 subjects randomized to the VBLOC group (i.e., the intent-to-treat group), there were six (6) SAEs related to the device, implant/revision, or therapy. This yielded an observed SAE rate of 3.7% (6/162, 95% CI: [1.4%, 7.9%]) among the VBLOC subjects, which met the primary safety endpoint, because the upper bound of this confidence interval is less than 15%. There were also nine (9) subjects who had SAEs related to the general surgical procedure. When these SAEs were counted as part of the primary safety endpoint, using an intent-to- treat analysis, the SAE rate was 8.6% (14/162), with a 95% CI of [4.8%, 14.1%], which also meets the performance goal of 15%. The Sham group did not experience any adverse events related to the general surgical procedure or related to the device, implant/revision, or therapy. There were no deaths or unanticipated adverse events among subjects enrolled in the ReCharge Study. The Serious Adverse Events are summarized in Table 13.

Table 13. Serious Adverse Events

Serious Adverse Events	VBLOC		Sham Control	
	N=162		N=7	7
	N (%)	N	N (%)	N
	Subjects	Events	Subjects	Events
SAE related to device, impla	ant/revision	ı, or ther	ару	
Neuroregulator malfunction	2 (1.2%)	2	0 (0.0%)	0
Atelectasis	1 (0.6%)	1	0 (0.0%)	0
Gallbladder disease	1 (0.6%)	1	0 (0.0%)	0
Emesis/vomiting	1 (0.6%)	1	0 (0.0%)	0
Pain, neuroregulator site	1 (0.6%)	1	0 (0.0%)	0
SAEs related to general sur	gical proce	dure		
Nausea	6 (3.7%)	6	0 (0.0%)	0
Cirrhosis*	1 (0.6%)	1	0 (0.0%)	0
Generalized ileus	1 (0.6%)	1	0 (0.0%)	0
Intra-operative oozing	1 (0.6%)	1	0 (0.0%)	0
SAEs related to pre-existing	g condition	or not re	lated	
Allergic reaction	1 (0.6%)	1	0 (0.0%)	0
Chest pain	1 (0.6%)	1	0 (0.0%)	0
Colitis	1 (0.6%)	1	0 (0.0%)	0
Gallbladder disease	1 (0.6%)	1	0 (0.0%)	0
Gastritis	0 (0.0%)	0	1 (1.3%)	1
Infection, other	1 (0.6%)	1	1 (1.3%)	1
Osteoarthritis	1 (0.6%)	1	0 (0.0%)	0
Pain, abdominal	1 (0.6%)	1	0 (0.0%)	0
Pain, other	2 (1.2%)	2	0 (0.0%)	0
Palpitations	1 (0.6%)	1	0 (0.0%)	0
Pericarditis	1 (0.6%)	1	0 (0.0%)	0
Breast cancer	0 (0.0%)	0	1 (1.3%)	1

Serious Adverse Events	VBLOC		VBLOC Sham Contro		ontrol
	N=162		N=7	7	
	N (%) N		N (%)	N	
	Subjects	Events	Subjects	Events	
Worsening back pain	0 (0.0%)	0	1 (1.3%)	1	

^{*}Subject not implanted.

Adverse Events in the Implanted Population

Five (5) subjects in the VBLOC arm and one (1) subject in the Sham control arm were enrolled in the ReCharge study, but did not receive device implantations. Using an analysis set that includes only those subjects who received the device implant, the most common adverse events (AEs) in the VBLOC Treatment group and those subjects randomized to the Sham Control group were pain and gastrointestinal (GI) symptoms, including heartburn, dysphagia, belching and nausea. AEs that occurred in \geq 5% of VBLOC and/or Sham control subjects through 12 and 18 months are summarized in Tables 14 and 15.

Table 14. Most common device, implant/revision procedure, or therapy related AEs through 12 months*

un ough 12 month	.5			
Adverse Event Type	VBLOC (n=157)		Sham (n=76)	
	Subjects	Events	Subjects	Events
Neuroregulator site pain	60 (38%)	72	32 (42%)	35
Other pain	38 (24%)	43	0 (0%)	0
Heartburn/dyspepsia	38 (24%)	42	3 (4%)	3
Other	34 (22%)	43	7 (9%)	10
Abdominal pain	20 (13%)	26	2 (3%)	2
Dysphagia	13 (8%)	13	0 (0%)	0
Eructation/belching	13 (8%)	13	0 (0%)	0
Nausea	7 (4%)	8	1 (1%)	1
Chest pain	9 (6%)	9	2 (3%)	2

^{*}Based on subjects with implanted device

Table 15. Most common device, implant/revision procedure, or therapy related AEs through 18 months*

Adverse Event Type	VBLOC (n=157)		Sham (n=76)	
	Subjects	Events	Subjects	Events
Neuroregulator site pain	60 (38%)	75	32 (42%)	36
Heartburn/dyspepsia	41 (26%)	45	3 (4%)	3
Other pain	41 (25%)	49	0 (0%)	0
Other	37 (24%)	46	7 (9%)	10
Abdominal pain	22 (14%)	30	2 (3%)	2
Eructation/belching	14 (9%)	14	0 (0%)	0
Chest pain	13 (8%)	13	2 (3%)	2
Dysphagia	13 (8%)	13	0 (0%)	0
Nausea	8 (5%)	11	1 (1%)	1
Abdominal cramps	8 (5%)	8	0 (0%)	0

^{*}Based on subjects with implanted device

Surgical removals of the device

Through 12 months, there were 13 surgical explants of the device for the subjects who withdrew from the trial, including eight (8) in the Sham control group and five (5) in the VBLOC treatment group. Reasons given for explants in the VBLOC arm included subject decision (n=2), pain when doing physical activity (n=1), pain at the neuroregulator site (n=1), and heartburn (n=1). In the Sham control arm, reasons given for device explants included subject decision (n=4), shoulder pain which required an MRI (n=1), worsening irritable bowel symptoms (n=1), need for mastectomy (n=1), and pain at the neuromodulator implant site (n=1).

Between the 12- and 18-month time points, there were 16 additional explants, including nine (9) in the Sham control group and 14 in the VBLOC treatment group. Twelve (12) explants in the VBLOC arm and seven (7) in the Sham arm were attributed to subject decision. Other reasons for device explant in the VBLOC arm included right arm pain (n=1), pain at the neuroregulator site (n=1), and upper quadrant pain (n=2). Other reasons for device explant in the Sham arm included the need for MRI for neck and back pain (n=1) and pain at the neuroregulator site (n=1).

Surgical revisions

Using per protocol analysis (i.e., those subjects who completed the study), eight (8) subjects (8/167, 4.8%) in the randomized VBLOC arm had nine (9) surgical revisions performed through 12 months: four (4) for device malfunction (2.4%), three (3) for pain at the neuroregulator site (1.8%), and two (2) for neuroregulator tilt (12.0%). There were no surgical revisions in the Sham control group.

Device explants between 12 and 18 months

Sixteen (16) patients in the VBLOC group had their device removed between 12 and 18 months after implant. Twelve (12) explants were for subject decision, one (1) for right arm pain due to thoracic outlet syndrome, one (1) for pain at the neuroregulator site, and two (2) for upper quadrant pain. Nine (9) patients in the Sham control group had their device removed between 12 and 18 months after implant. Seven (7) explants were for subject decision, one (1) for need for MRI for neck and back pain, and one (1) due to pain at the neuroregulator site.

2. Effectiveness Results

The analysis of effectiveness was based on the 233 evaluable at the 12 month time point. Key effectiveness outcomes are presented in Figure 3.

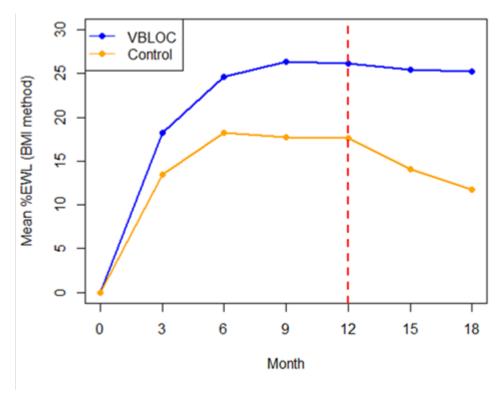


Figure 3. Percent Excess Weight loss (%EWL) in VBLOC and Control Arms through 18 months. The dashed red line indicates the 12 month time point of the primary analysis of %EWL in the ReCharge trial.

The first co-primary effectiveness endpoint was percent excess weight loss (%EWL) at 12 months after randomization, with ideal body weight calculated using the BMI method (i.e., the weight a subject would have with a BMI of 25 kg/m²). The goal of the analysis of this co-primary endpoint was to show that the mean %EWL in the VBLOC group is at least 10% greater than the %EWL in the Sham control group (i.e., there was a pre-specified super-superiority margin of 10%). Using the intent-to-treat study population (i.e., all subjects who enrolled in the study), the average %EWL at 12 months was 24.4% (SD=23.6%) in the VBLOC group and 15.9%

(SD=17.7%) in the Sham control group, resulting in an average difference between the VBLOC and sham control groups of 8.5% (95% CI: [3.1%, 13.9%]). While these results would support a conclusion that average %EWL is higher in the VBLOC group than in the Sham control group, the pre-specified superiority margin of 10% was not achieved, because the lower bound of the confidence interval is less than 10%.

At 18 months, the observed mean %EWL in the VBLOC group was 25.2% (95% CI: [20.6, 29.8]) and 11.7% (95% CI: [5.4, 18.0]) in the Sham control group, resulting in a treatment difference of 13.5% (95% CI: [5.7, 21.3]). Figure 3 shows the %EWL through 18 months. Analysis of the 18-month data from the ReCharge study suggests maintenance of the weight loss at 12 months.

The second co-primary effectiveness endpoint had two (2) requirements: (i) at least 55% of VBLOC subjects would achieve a %EWL of at least 20%; and (ii) at least 45% of VBLOC subjects would achieve a %EWL of at least 25%. The assessments of these objectives were based on observed rates. According to the protocol both of these objectives should be met for trial success. This co-primary objective was also not achieved: (i) 52.5% (<55%) of VBLOC subjects had a %EWL of at least 20%; and (ii) 38.3% (<45%) of VBLOC subjects had a %EWL of at least 25%. The Sham control group had 32.5% (n=25) of subjects with 20% (n=18) or greater EWL and 23.4% of subjects with 25% or greater EWL.

Although the study did not include a pre-determined endpoint for factors associated with health improvements, data were collected on the 12 month change in parameters such as cholesterol, triglycerides, blood pressure, fasting glucose, and HbA1c. Results suggested that there were small improvements of various parameters in both the VBLOC group and the Sham control group from baseline to 12 months, but the change in the VBLOC group was not statistically significantly different from the change in the Sham control group (Table 16).

Table 16. Summary of factors associated with co-morbidities at screening, month 12, and changes from screening to month 12.

Parameter	Study Visit	VBLOC Mean ± SD (N Subjects)	Sham Mean ± SD (N Subjects)	Difference (VBLOC – Sham) Mean ± SD
Systolic Blood Pressure	Screening	127.9 ± 12.5 (162)	129.9 ± 12.8 (77)	
	Month 12	$121.9 \pm 11.8 (147)$	125.5 ± 15.7 (66)	
	Change	-5.5 ± 14.2 (147)	-4.0 ± 13.5 (66)	-1.5 ± 14.0

Parameter	Study Visit	VBLOC Mean ± SD (N Subjects)	Sham Mean ± SD (N Subjects)	Difference (VBLOC – Sham) Mean ± SD
Diastolic Blood Pressure	Screening	80.7 ± 8.8 (162)	82.3 ± 10.2 (77)	
	Month 12	$77.9 \pm 8.1 (147)$	$77.1 \pm 9.2 (66)$	
	Change	$-2.8 \pm 9.6 (147)$	$-4.5 \pm 8.2 (66)$	1.7 ± 9.2
Fasting Glucose (mg/dL)	Screening	96.3 ± 17.3 (131)	98.6 ± 30.0 (55)	
	Month 12	$94.5 \pm 15.8 (123)$	$97.6 \pm 29.9 (51)$	
	Change	-2.0 ± 14.9 (122)	-0.6 ± 10.3 (49)	-1.4 ± 13.7
HbA1c (%)	Screening	$5.7 \pm 0.6 (142)$	5.8 ± 1.3 (65)	
	Month 12	$5.3 \pm 0.5 (137)$	5.5 ± 1.0 (60)	
	Change	$-0.3 \pm 0.4 (135)$	$-0.3 \pm 0.5 (60)$	-0.0 ± 0.4
LDL Cholesterol (mg/dL)	Screening	121.5 ± 31.6 (143)	120.0 ± 26.5 (65)	
	Month 12	$115.9 \pm 29.6 (137)$	$117.8 \pm 30.8 (60)$	
	Change	$-6.2 \pm 26.2 (136)$	-3.4 ± 23.5 (60)	-2.8 ± 25.4
HDL Cholesterol (mg/dL)	Screening	54.2 ± 14.1 (143)	52.2 ± 14.5 (65)	
	Month 12	55.7 ± 13.7 (137)	53.1 ± 14.1 (60)	
	Change	$1.2 \pm 9.4 (136)$	0.6 ± 8.4 (60)	0.6 ± 9.1
Triglycerides	Screening	$136.9 \pm 58.9 (143)$	$151.5 \pm 95.4 (65)$	
	Month 12	$115.9 \pm 58.5 (137)$	$117.9 \pm 62.6 (60)$	
	Change	-21.6 ± 57.1 (136)	-33.1 ± 61.5 (60)	11.5 ± 58.5

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 24 investigators. None of the clinical investigators had disclosable financial interests/ arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Additional pre-specified effectiveness endpoints included percentage of total body weight loss (%TBL), Impact of Weight on Quality of Life (IWQOL-Lite), Three Factor Eating Questionnaire (TFEQ), and Beck Depression Inventory (BDI-II). For the first factor (Cognitive Restraint), both VBLOC and Sham Control Groups experienced an increase from baseline to month 12, which means there was improved self-restraint in limiting food intake. For the second factor (Disinhibition), both groups had a decrease from baseline to month 12, which means that subjects were less likely to lose control over food intake (i.e., less likely to overeat or binge eat). For the third factor (Hunger), the scores in both groups improved from baseline to month 12 reflecting a decrease level of hunger.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on June 17, 2014, the Gastroenterology and Urology Devices Panel voted 8 to 1 that there is a reasonable assurance the device is safe, 4 to 5 that there is a reasonable assurance that the device is effective, and 6 to 2 (with 1 abstention) that the benefits of the device do outweigh the risks in patients who meet the criteria specified in the proposed indication.

The Panel raised concerns that the majority of patients who were evaluated in the ReCharge pivotal study were Caucasian and female. To address this concern, the new enrollment PAS now has the following goal: A minimum of 40 subjects enrolled in the registry, or 20% of the post-market cohort, will be from minority racial and ethnic groups. Additionally, a minimum of 40 male subjects will be enrolled.

The Panel also raised concerns that the implantable components are unsafe for MRIs. The revised labeling not only lists the need for an MRI as a contraindication, but also provides more detailed explanations on what MRI related risks could be. By way of example, the patient labeling states, "The Maestro System is not safe for

use with MRI scans. Use of Magnetic Resonance (MR) could deliver energy to your implanted device. This may cause tissue damage resulting in injury."

The Panel meeting summary can be found at:

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/Gastroenterology-UrologyDevicesPanel/UCM401760.pdf

B. FDA's Post-Panel Action

Following the Panel meeting, EnteroMedics provided additional, clarifying information that was requested by FDA on electromagnetic compatibility testing and device sterilization. In addition, the Indications for Use statement was revised to more accurately reflect the age and BMI categories of the patients who participated in the ReCharge study. Based on input from the Panel members, device labeling was revised to include contraindications and warnings relating to the adverse events observed in the Recharge study and risks relating to exposure to EMC, EMI and MRI.

The Panel's findings were that the ReCharge study demonstrated safety, but did not demonstrate effectiveness since the co-primary endpoints were not met. However, since there were significant improvements in weight loss in the VBLOC Group when compared to the Sham Control Group (although super-superiority was not demonstrated), the panel advised that the benefits outweigh the risks. When taking into consideration all three (3) recommendations from the Panel, the majority of the FDA review team recommends approval for this device, including EnteroMedics agreeing to conduct two (2) five-year post-approval studies.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. <u>Effectiveness Conclusions</u>

The clinical study had two (2) co-primary effectiveness endpoints, with neither endpoint being met. The first co-primary endpoint specified that the device would achieve a mean percent excess weight loss (%EWL) that was at least 10% greater than the Sham Control Group's mean %EWL. The average %EWL at 12 months was 24.4% (SD=23.6%) in the VBLOC Group and 15.9% (SD=17.7%) in the Sham Control Group, resulting in an average difference between the VBLOC Group and Sham Control Group of 8.5% (95% CI: [3.1%, 13.9%]). While the average %EWL was higher in the VBLOC Group than in the Sham Control Group, the pre-specified superiority margin of 10% was not achieved.

EnteroMedics also provided 18 month data for %EWL. These data were limited because of incomplete follow-up (follow-up rates of 72.2% and 54.5% in the VBLOC Group and Sham Control Group, respectively), and breaking of the blind in the Sham Control Group after 12 months (most subjects were unblinded at the 16 month visit or after). At 18 months, the observed mean %EWL in the VBLOC Group was 25.2% (95% CI: [20.6, 29.8]) and 11.7% (95% CI: [5.4, 18.0]) in the Sham Control Group, resulting in a treatment difference of 13.5% (95% CI: [5.7, 21.3]).

The second co-primary effectiveness endpoint had two (2) requirements: (i) at least 55% of VBLOC subjects needed to achieve a %EWL of at least 20% and (ii) at least 45% of VBLOC subjects needed to achieve a %EWL of at least 25%. The assessments of these objectives were based on observed rates rather than statistical hypothesis tests and according to the protocol both of these objectives should be met for trial success. Neither of the co-primary objectives was met: (i) 52.5% (<55%) of VBLOC subjects had a %EWL of at least 20% and (ii) 38.3% (<45%) of VBLOC subjects had a %EWL of at least 25%.

It should be noted that, although the pre-specified super-superiority endpoints for effectiveness were not met, results demonstrate that weight loss, as measured by %EWL, was significantly greater in the VBLOC Group than the %EWL in the Sham Control Group at the 12-month time point. Additionally, the mean %EWL in VBLOC subjects was maintained at the 18-month time point. With regard to the data on improvements in lab measurements associated with obesity (e.g., HbA1c, cholesterol), both VBLOC and Sham Control Groups experienced small improvements in some parameters, which could have been attributable to weight management alone (e.g., weight loss counseling), but not specifically to VBLOC therapy.

B. Safety Conclusions

EnteroMedics conducted a series of nonclinical tests, including electrical safety to demonstrate essential performance and conformance to design controls; electromagnetic compatibility to demonstrate immunity from radiated electromagnetic fields; battery abuse testing; tensile strength, mechanical shock and abrasive wear of the implantable components; sterility and biocompatibility testing in accordance with validated test protocols and pass/fail criteria; and in vivo porcine studies with device implantation and VBLOC therapy. Results support the safety of the device.

The risks of the device are based on nonclinical, as well as data collected in clinical studies conducted to support PMA approval as described above.

The primary safety endpoint of the ReCharge trial was to demonstrate that the 12-month serious adverse event (SAE) rate related to implant or revision procedures, device, or therapy was less than a performance goal of 15% among the subjects in the VBLOC Group. There were six (6) SAEs identified in these categories, which led to an observed SAE rate of 3.7% (6/162, 95% CI: [1.4%, 7.9%]) among the VBLOC subjects, which met the primary safety endpoint because the upper bound of this confidence interval is less than 15%. There were also nine (9) subjects who had SAEs related to the general surgical procedure. When these SAEs were counted as part of the primary safety endpoint, using an intent-to- treat analysis, the updated SAE rate was 8.6% (14/162), with a 95% CI of [4.8%, 14.1%], which also meets the performance goal of 15%.

One important safety consideration is that the MAESTRO RNR and leads are permanently implanted and the device is labeled as unsafe for MRI. Therefore, removal of the device in order to receive an MRI, or for other medical or personal reasons, would require additional surgery. Concerns have been raised on the ease of removing the leads/electrodes from the abdominal vagus nerve trunks. To address this concern, the device labeling contains prominent warnings that the MAESTRO® System is MR unsafe. Although not observed during the course of the ReCharge clinical trial, adverse events relating to device explantation will be followed in the two (2) planned post-approval studies.

The need for additional surgical revisions related to AEs and device malfunctions in the 12 to 18 month period is of some concern and will need to be monitored closely. An additional concern will be the need for additional surgical explantation as a result of adverse events or ineffective treatment. The ability to safely and totally remove the device even after a long period of use will be of critical importance.

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical studies conducted to support PMA approval as described above. The probable benefits of the device are also based on data collected in clinical studies conducted to support PMA approval as described above, and is based on a demonstration of moderate, but sustained weight loss through 18 months post-implant. The majority of serious adverse events observed in the ReCharge trial were surgery-related and resolved over time.

Additional factors to be considered in determining probable risks and benefits for the MAESTRO[®] Rechargeable System included the limited options currently available for treatment of morbid obesity. FDA's recommendation for Approval of the MAESTRO[®] Rechargeable System is based in part on an understanding that both patients and clinicians are in need of more therapeutic options for treating obesity.

In conclusion, given the available information above, the data supports the intended use of the MAESTRO[®] Rechargeable System for treatment of morbid obesity and

the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Despite not achieving either co-primary endpoint, the overall mean %EWL for the VBLOC Group was 24.4%. The 15.9% EWL for the Sham Control Group exceeded expectations and resulted in a lower super superiority margin than anticipated.

The finding that over 50% of the VBLOC Group subjects achieved at least a 20% EWL also shows that this device is likely to be clinically effective. Finally, the adverse event profile for the MAESTERO[®] Rechargeable System is consistent with a demonstration of device safety, with only a small number of SAEs which were primarily related to discomfort at the neuroregulator site. The supplemental data provided by EnteroMedics, Inc. for the 12 to 18 month interval shows that the weight loss in the VBLOC treated subjects is durable through that time frame. Overall, there is little change in the prevalence of adverse events between the 12 month and cumulative 18 month data.

In conclusion, the benefit-risk model profile favors the approval of this device.

XIV. CDRH DECISION

CDRH issued an approval order on January 14, 2015. The final conditions of approval cited in the approval order are described below.

1. Maestro Extended Follow-up of the Premarket Cohort (ReCharge Clinical Trial): This is a multicenter, single-arm prospective, longitudinal study designed to gather long-term data on adverse events, weight loss, surgical revisions and explants, and change in obesity-related comorbidities. This study will continue to follow patients from the ReCharge pivotal study for 5 years post Maestro implantation. A total of 210 subjects are available for the extended follow-up study and will be invited to participate in the PAS. At 5 years, a minimum of 105 patients (50% of enrolled subjects) are expected to still be implanted with the device and attend the 5-year clinic visit. It is estimated that the remaining 105 patients will have been explanted prior to the 5-year visit and approximately 50% of the explanted patients will agree to provide additional follow-up data after explant.

The primary safety objective is to show that the rate of SAEs related to the device, implant/revision procedure (including explant procedure), general surgical procedure, or therapy algorithm is lower than 25% at 5 years. The hypothesis test for the primary safety objective will be evaluated using the Kaplan-Meier estimate of the 5-year SAE rate. The endpoint will be met if the estimate for the upper 95% loglog confidence limit is lower than 25% at 5 years. Assuming a 25% performance goal, 1-sided 0.05 type-I error rate, expected 5-year related SAE rate of 15%, and an

8% rate of censoring per year from implant/crossover, it was estimated that the objective would be powered at the 80% level.

Other study endpoints include: weight loss measured by %EWL and %TBL; change in obesity-related comorbidities (blood pressure, lipid levels, triglycerides, blood glucose, HbA1c and waist circumference); and 5-year rates of surgical revision, device explant, device explants specifically to undergo MRI, therapy-related AEs, and device (neuroregulator or lead) malfunction requiring a revision procedure; and AEs involving lead breakage/fracture, twisting/entanglement, replacement, lead erosion, and bowel/tissue obstruction.

2. Maestro New Enrollment Study: This is a prospective, 5-year, multicenter, single-arm study of the Maestro Rechargeable System. A total of 200 subjects will be enrolled at 15 centers (minimum of 10 centers) in the United States. The study will enroll a minimum of 40 subjects (20% of postmarket cohort) from minority racial and ethnic groups and also a minimum of 40 male subjects.

The primary objective is to evaluate the long-term safety of Maestro in patients at least 18 years old who have a BMI of 40-45 kg/m², or a BMI of 35-39.9 kg/m² with 1 or more obesity related comorbidities and have failed at least 1 supervised weight management program in the past 5 years. Specifically, the study will assess the rate of SAEs related to the device, implant/revision procedure (including explant procedure), general surgical procedure, or therapy at 5 years. Other study endpoints include: weight loss measured by %TBL and %EWL; change in obesity-related comorbidities (blood pressure, waist circumference and the number, type and dose of medications for treatment of diabetes, hypertension and dyslipidemia); surgical revision, surgical explant, device explants specifically to undergo MRI, therapy-related AEs, and device (neuroregulator or lead) malfunction requiring a revision procedure; and AEs involving lead breakage/fracture, twisting/entanglement, replacement, lead erosion, and bowel/tissue obstruction. In addition physician training objectives include evaluation of surgical revision rates and implant procedure times by physician and site.

At 5 years, a minimum of 120 patients (60% of 200 enrolled subjects) are expected to still be implanted with the device and attend the 5-year clinic visit. It is estimated that the remaining 80 patients will have been explanted prior to the 5-year visit and approximately 50% of the explanted patients will agree to provide additional follow-up data after explant.

The primary safety objective is to demonstrate that the rate of SAEs related to the device, implant/revision procedure (including explant procedure), general surgical procedure, or therapy is statistically lower than 25% at 5 years. The endpoint will be met if the estimate for the upper 95% log-log confidence limit is lower than 25% at 5 years. Assuming a 25% performance goal, one-sided 0.025 type-I error rate, expected 5-year related SAE rate of 15%, and an 8% rate of explant/dropout per year, it was estimated that the primary safety objective would have at least 90%

power with 200 enrolled subjects.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. <u>REFERENCES</u>

- 1. ASGE/ASMBS Task Force on Endoscopic Bariatric Therapy (2011) A pathway to endoscopic bariatric therapies. Gastroint Endosc 74: 943-953.
- 2. Pisapia JM, Halpern CH, Williams NN, Wadden TA, Baltuch GH, Stein SC (2010) Deep brain stimulation compared with bariatric surgery for the treatment of morbid obesity: a decision analysis study. Neurosurg Focus 29:E15